

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 03/082889 A1

- (51) International Patent Classification⁷: **C07H 17/08** [KR/KR]; Kungang Apt. 1103-302, #213, Kumi-dong, Bundang-gu, 463-500 Seongnam-si, Kyungki-do (KR).
(21) International Application Number: **PCT/KR02/00588** **SUH, Kwee Hyun** [KR/KR]; Daewoo 2-cha Apt. 205-1301, #244-3, Jeungpo-dong, 467-110 Icheon-si, Kyungki-do (KR).
(22) International Filing Date: **3 April 2002 (03.04.2002)**
(25) Filing Language: **Korean** (74) Agents: **JANG, Seong Ku** et al.; 17th Fl., KEC Building, #275-7, Yangjae-dong, Seocho-ku, Seoul 137-130 (KR).
(26) Publication Language: **English** (81) Designated States (*national*): **CN, JP, US**.
(71) Applicant (*for all designated States except US*): **HANMI PHARM. CO., LTD.** [KR/KR]; #893-5, Hajeo-ri, Paltan-myeon, Hwaseong-gun, Kyungki-do 445-910 (KR). (84) Designated States (*regional*): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).
(72) Inventors; and **Published:**
(75) Inventors/Applicants (*for US only*): **KIM, Gi Jeong** — *with international search report*
[KR/KR]; #493-141, Sinnae-dong, Jungrang-gu, Seoul 131-130 (KR). **SEONG, Mi Ra** [KR/KR]; Halla Apt. 305-1005, #181, Kungok-dong, Bundang-gu, 463-725 Seongnam-si, Kyungki-do (KR). **YUN, Sang Min**
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/082889 A1

(54) Title: **PROCESS OF PREPARING AZITHROMYCIN AND CRYSTALLINE 9-DEOXO-9A-AZA-9A-HOMOERY-THROMYCIN A HYDRATE USED THEREIN**

(57) Abstract: Azithromycin is prepared in a high yield by a simple process using a crystalline 9-deoxo-9a-aza-9a-homoery-thromycin A hydrate.

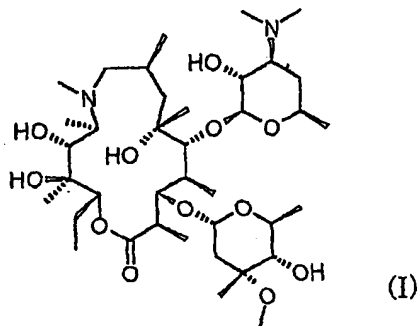
**PROCESS OF PREPARING AZITHROMYCIN AND
CRYSTALLINE 9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A
HYDRATE USED THEREIN**

5 **FIELD OF THE INVENTION**

The present invention relates to a method of preparing azithromycin using a crystalline 9-deoxo-9a-aza-9a-homoerythromycin A hydrate as an intermediate, and a novel precursor thereof, crystalline 9-deoxo-9a-aza-9a-homoerythromycin A hydrate, and a process for the preparation thereof.

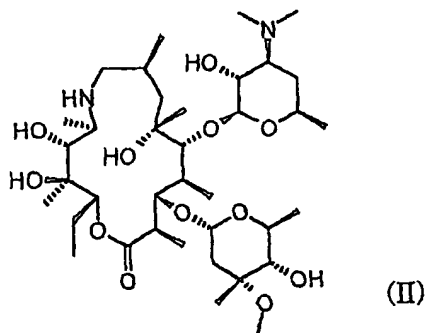
BACKGROUND OF THE INVENTION

Azithromycin, 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A (IUPAC name: N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A), is an azalide-based semisynthetic macrolide antibiotic of formula (I) which is very effective in treating respiratory organ diseases, sexual contact infection, skin infection diseases and the like, as disclosed in US Patent Nos. 4,517,359 and 4,474,768 (Kirst and Sides, *Antimicrob. Agents Chemother.*, 33, 1419(1989)):



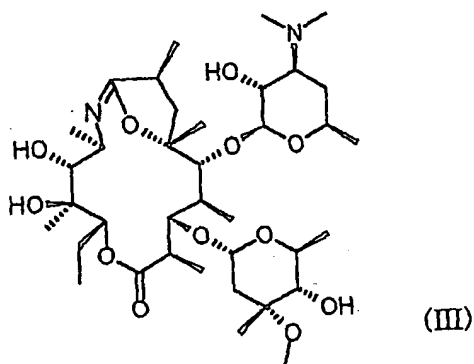
Generally, azithromycin is prepared by conducting conventional Eschweiler-Clarke reductive N-methylation (Eschweiler and Clarke, *Org. React.*, 5, 290(1945)) of the 9a-position of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II), as described in US Patent No. 4,517,359, or by protecting the 3'-nitrogen of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II) with N-oxide, conducting N-methylation of the 9a-position thereof and then removing

the N-oxide protecting group, as described in US Patent No. 4,474,768. The compound of formula (II) is thus a very important precursor in the preparation of azithromycin.



5

9-Deoxo-9a-aza-9a-homoerythromycin A of formula (II) may be prepared by reducing 9-deoxo-6-deoxy-6,9-epoxy-9,9a-didehydro-9a-aza-homoerythromycin A (simply, 6,9-imino ether) of formula (III) which is prepared from erythromycin A 9-oxime in accordance with a conventional method (Djokic et al., *J. Chem. Soc. Perkin Trans. I*, 1881(1986)).



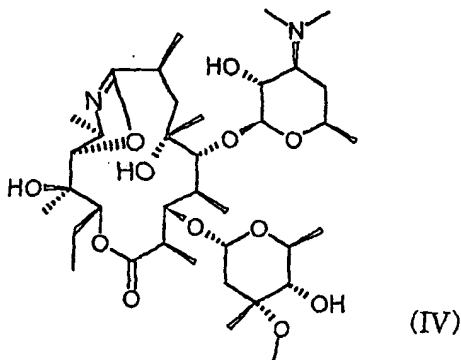
For example, US Patent Nos. 4,328,334 and 6,013,778 disclose a method of preparing the compound of formula (II) from the compound of formula (III) by way of conducting hydrogenation under a high hydrogen pressure in the presence of a rhodium(Rh), platinum(Pt), palladium(Pd) or ruthenium(Ru) metal or metal oxide catalyst; and Austrian Patent No. 8,600,536, by way of conducting electrical reduction. However, these methods have the problem that they require the use of an expensive precious metal catalyst and a high hydrogen pressure of 65 psi or

15
20

higher, or that electrical reduction is not suitable for mass-production.

US Patent No. 4,328,334 discloses a method of preparing the compound of formula (II) by reducing the compound of formula (III) in a methanol solution maintained at 4°C with a reducing agent such as NaBH₄. However, this method
5 requires a large excess amount of NaBH₄ (16 mole equivalents or more) and the reduction product existing in the form of a borate complex must be subjected to further hydrolysis using an inorganic acid such as hydrochloric acid, the hydrolysis reaction inducing a side reaction to produce a large quantity of impurities (Djokic et al., *J. Chem. Soc. Perkin Trans. I*, 1881(1986)).

10 International Publication Patent No. WO 94/26758 teaches that 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II) may be prepared by hydrogenating erythromycin A 9-oxime or 9-deoxo-11-deoxy-9,11-epoxy-9,9a-didehydro-9a-aza-homoerythromycin (simply, 9,11-imino ether) of formula (IV) prepared from 6,9-imino ether of formula (III) under a high pressure in the
15 presence of PtO₂. However, this method suffers from a high manufacturing cost.



20 Therefore, there exists a demand for a simple method which is capable of providing 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II) in a simple, economic way.

Accordingly, the present inventors have endeavored to develop such a method and have found that pure crystalline hydrate of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II) can be prepared in a high yield by
25 reducing 6,9-imino ether of formula (III) with a small amount of NaBH₄ at -20 to -10°C and treating the reaction mixture with an acidic solution of citric acid, followed by neutralization.

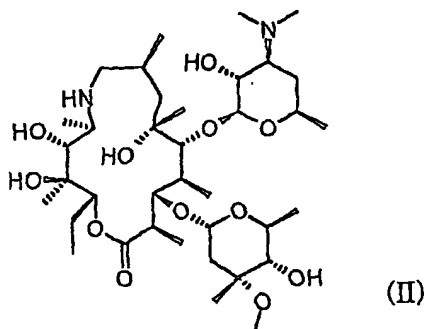
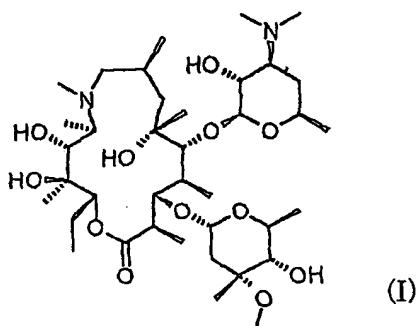
SUMMARY OF THE INVENTION

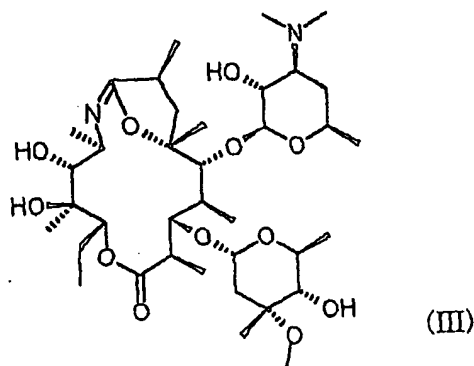
Accordingly, it is a primary object of the present invention to provide a simple, high-yield process for preparing azithromycin.

- 5 It is another object of the present invention to provide a crystalline 9-deoxo-9a-aza-9a-homoerythromycin A hydrate used as a precursor in the preparation of azithromycin, and a process for the preparation thereof.

In accordance with one aspect of the present invention, there is provided a method of preparing azithromycin of formula (I) comprising the steps of: (a)
10 reducing 6,9-imino ether of formula (III) dissolved in methanol with 5 to 7 mole equivalents of NaBH_4 at -20 to -10°C , treating the reaction mixture with an acidic aqueous acetone solution of citric acid, and adjusting the solution pH to 10.5 to 12.0 to obtain a crystalline hydrate of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II); and

- 15 (b) N-methylating the compound of formula (II) prepared in step (a) with an aqueous formaldehyde-formic acid mixture in an organic solvent:





In accordance with another aspect of the present invention, there is provided a crystalline hydrate of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II) used as a precursor in the preparation of azithromycin; and a method of preparing same comprising the steps of: (i) reducing 6,9-imino ether of formula (III) dissolved in methanol with 5 to 7 mole equivalents of NaBH₄ at -20 to -10°C, (ii) treating the reaction mixture with an acidic aqueous acetone solution of citric acid, and (iii) adjusting the solution pH to 10.5 to 12.0.

10 BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects and features of the present invention will become apparent from the following description of the invention taken in conjunction with the following accompanying drawings, which respectively show:

FIG. 1: a powder X-ray diffraction scan of the crystalline 9-deoxo-9a-aza-9a-homoerythromycin A hydrate prepared in accordance with the inventive method; and

FIG. 2: a powder X-ray diffraction scan of 9-deoxo-9a-aza-9a-homoerythromycin A prepared in accordance with a conventional method.

DETAILED DESCRIPTION OF THE INVENTION

The method of the present invention is described in detail as follows:

25 **Step (a)**

A methanol solution of the 6,9-imino ether of formula (III) prepared, e.g., by a conventional method (Djokic et al., *J. Chem. Soc. Perkin Trans. I*,

1881(1986)) is chilled to -20 to -10°C , NaBH_4 is added thereto in an amount ranging from 5 to 7 mole equivalents based on the amount of the 6,9-imino ether, and then stirred at the same temperature for a period ranging from 4 to 6 hrs. After completion of the reduction reaction, the reaction solution is concentrated,
5 water and an organic solvent such as dichloromethane, chloroform and 1,2-dichloroethane are added to the resulting residue, and then the organic layer is separated and concentrated.

To the resulting residue, water and acetone are added, followed by adding citric acid in an amount ranging from 1 to 20 mole equivalents based on
10 the amount of the 6,9-imino ether. The pH of the mixture is adjusted to 2.0 to 3.0 with HCl at a temperature of 0°C to room temperature, and stirred for at least 30 min. As can be confirmed by thin layer chromatography, citric acid hydrolyzes the borate complex of the reduction product efficiently without inducing undesirable side reaction. Then, the solution pH is adjusted to 10.5 to
15 12.0 at a temperature of 0°C to room temperature to induce precipitation of crystals. The precipitated crystals are filtered and dried at 40°C to give a pure monohydrate form of crystalline hydrate of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II) having a melting point of 126 to 130°C and a moisture content of 2.0 to 3.5% (determined by Kaal-Fisher moisture
20 measurement) in a high yield of 85% or higher. The amount of acetone used is preferably in the range of 1 to 5 ml per 1 g of the compound of formula (III), and water, in a volume ranging from 1 to 4 folds of the acetone volume.

If necessary, the crystalline hydrate of formula (II) thus obtained may be further recrystallized from a mixed solvent of water and an organic solvent
25 such as acetone, methanol and acetonitrile to improve the purity thereof. Preferably, the pH of the recrystallized solution is adjusted to 10.5 or higher, and the amount of the organic solvent used is in the range of 1 to 2 ml per 1 g of the crystalline hydrate, the water to organic solvent volume ratio being in the range of 1 to 4.

30 The crystalline hydrate of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II) obtained in accordance with the present invention is completely free of boron-containing impurities and it is a novel compound which is characteristically different from the well-known, amorphous anhydrous 9-deoxo-9a-aza-9a-homoerythromycin A prepared by prior methods (US Patent Nos.
35 4,328,334 and 6,013,778, and International Publication Patent No. 94/26758) as

judged by its melting point, moisture content and powder X-ray diffraction pattern, as shown in Table.

Table

Physical properties	Inventive powder	Conventional powder
Shape	Crystalline powder	Amorphous powder
Melting point	126 - 130°C	113 - 116°C
Moisture content	2.0 - 3.5%	Below 1%
2 theta value of powder X-ray diffraction peaks (I/I ₀ ≥ 10)	7.700° ± 0.2, 8.080° ± 0.2, 10.080° ± 0.2, 11.440° ± 0.2, 12.200° ± 0.2, 13.840° ± 0.2, 14.100° ± 0.2, 14.520° ± 0.2, 14.820° ± 0.2, 15.140° ± 0.2, 15.800° ± 0.2, 16.780° ± 0.2, 17.260° ± 0.2, 18.160° ± 0.2, 18.900° ± 0.2, 19.180° ± 0.2, 19.800° ± 0.2, 21.040° ± 0.2	No observable diffraction peaks

5 Step (b)

In accordance with the present invention, the crystalline hydrate of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II) obtained in step (a) is subjected to conventional Eschweiler-Clarke reductive N-methylation (Eschweiler and Clarke, *Org. React.*, 5, 290(1945)), i.e., reacted with a formic acid-aqueous formaldehyde mixture in an organic solvent which may be a halogenized solvent such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; an alcohol such as methanol, ethanol and isopropanol; a ketone such as acetone, ethylmethylketone and isobutylmethylketone; and an ester such as methyl acetate, ethyl acetate and isopropyl acetate, to give azithromycin of formula (I) in a high yield of at least 90%. The amounts of formic acid and formaldehyde used are each independently in the range of 1 to 3 mole equivalents based on the amount of the crystalline hydrate of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II), and the reaction may be performed at a temperature ranging from room temperature to the boiling point of the solvent.

The following Examples are given for the purpose of illustration only, and are not intended to limit the scope of the invention.

Example 1: Preparation of crystalline 9-deoxo-9a-aza-9a-homoerythromycin A hydrate

27.31 g (37.4 mmol) of 9-deoxo-6-deoxy-6,9-epoxy-9,9a-didehydro-9a-aza-homoerythromycin A (6,9-imino ether) prepared by a conventional method (Djokic et al., *J. Chem. Soc. Perkin Trans. I*, 1881(1986)) was dissolved in 150 ml of methanol and then cooled to -15°C . 8.40 g (222.1 mmol) of NaBH_4 is added thereto in small portions and stirred at -15°C for 4 hrs. The mixture was then slowly heated to room temperature and concentrated under reduced pressure. Then, chloroform and water were added to the resulting residue, the organic layer was separated and concentrated. 100 ml of water and 60 ml of acetone were poured to the resulting residue, and 23.1 g (109.9 mmol) of citric acid monohydrate was added thereto. After citric acid was dissolved, pH of the solution was adjusted to 2.5 with 6N-hydrochloric acid and stirred at room temperature for 30 min. The resulting solution was cooled to below 10°C , 20% sodium hydroxide was slowly added thereto to adjust the pH to 11.5, and stirred at the same temperature for 1 hr. The precipitated crystals were filtered, washed with cold water and dried at 40°C overnight to obtain 23.5 g of the title compound (yield: 85.5%).

m.p.: $126-130^{\circ}\text{C}$

moisture content : 2.5%

2θ values of powder X-ray diffraction peaks ($I/I^{\circ} \geq 10$) : $7.700^{\circ} \pm 0.2$, $8.080^{\circ} \pm 0.2$, $10.080^{\circ} \pm 0.2$, $11.440^{\circ} \pm 0.2$, $12.200^{\circ} \pm 0.2$, $13.840^{\circ} \pm 0.2$, $14.100^{\circ} \pm 0.2$, $14.520^{\circ} \pm 0.2$, $14.820^{\circ} \pm 0.2$, $15.140^{\circ} \pm 0.2$, $15.800^{\circ} \pm 0.2$, $16.780^{\circ} \pm 0.2$, $17.260^{\circ} \pm 0.2$, $18.160^{\circ} \pm 0.2$, $18.900^{\circ} \pm 0.2$, $19.180^{\circ} \pm 0.2$, $19.800^{\circ} \pm 0.2$, $21.040^{\circ} \pm 0.2$

Example 2: Purification of crystalline 9-deoxo-9a-aza-9a-homoerythromycin A hydrate

20 g of the crystalline 9-deoxo-9a-aza-9a-homoerythromycin A hydrate obtained in Example 1 was dissolved in 30 ml of acetone, and 90 ml of water was added thereto at room temperature. The solution pH was adjusted to above 10.5 with a dilute sodium hydroxide solution, cooled to below 10°C and stirred for 1 hr. The precipitated crystals was filtered, washed with cold water and dried at 40°C overnight to obtain 18.8 g of a purified form of the title compound (recovery: 94%).

Example 3: Purification of crystalline 9-deoxo-9a-aza-9a-homoerythromycin A hydrate

The procedure of Example 2 was repeated except that methanol was used instead of acetone, to obtain a purified form of the title compound
5 (recovery: 90%).

Example 4: Purification of crystalline 9-deoxo-9a-aza-9a-homoerythromycin A hydrate

The procedure of Example 2 was repeated except that acetonitrile was
10 used instead of acetone, to obtain a purified form of the title compound (recovery: 92%).

Example 5: Preparation of azithromycin

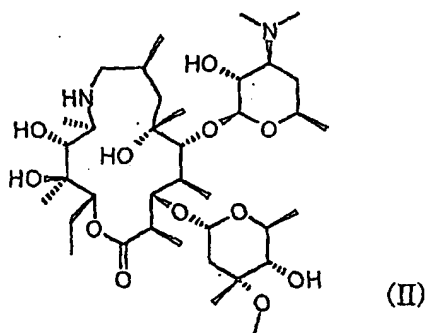
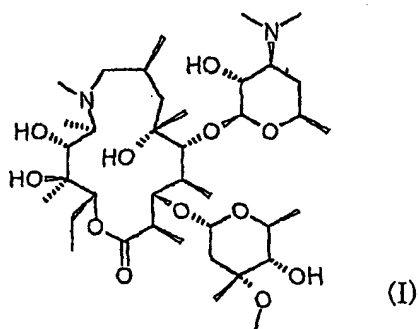
22.05 g (30.0 mmol) of the crystalline 9-deoxo-9a-aza-9a-
15 homoerythromycin A hydrate obtained in Examples 1 to 4 was dissolved in 100 ml of chloroform, 2.3 ml of formic acid and 4.7 ml of a 35% aqueous formaldehyde solution were added thereto, and refluxed for 7 hrs. The reaction solution was cooled to room temperature, 100 ml of water was added thereto, and the pH was adjusted to 2.5 with 6N-hydrochloric acid. The
20 organic layer was removed. 150 ml of chloroform was added to the aqueous layer, the pH was adjusted to 11.0 with a dilute sodium hydroxide solution, and the organic layer was separated. The organic layers were combined, concentrated under a reduced pressure, and the resulting residue was recrystallized from an ethanol-water mixture. The resulting crystals were
25 filtered, washed with water and dried at 45°C to obtain 20.2 g of the title compound (yield: 90%).

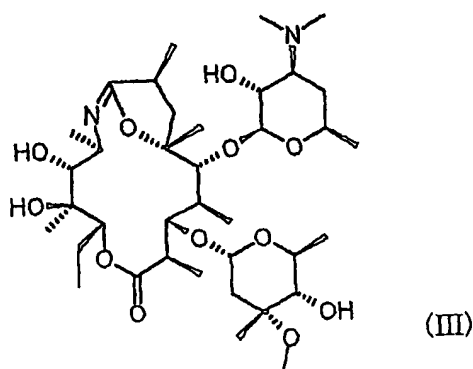
As shown above, the method of the present invention is simple and gives azithromycin in a high yield.

30 While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

WHAT IS CLAIMED IS :

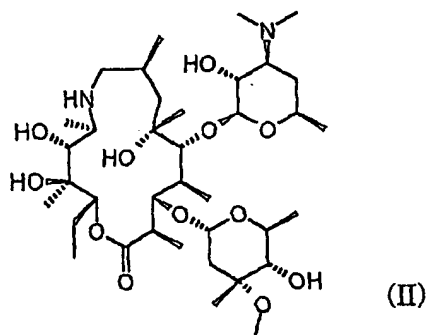
1. A method of preparing azithromycin of formula (I) comprising the steps of: (a) reducing 6,9-imino ether of formula (III) dissolved in methanol with 5 to 7 mole equivalents of NaBH_4 at -20 to -10°C , treating the reaction mixture with an acidic aqueous acetone solution of citric acid, and adjusting the solution pH to 10.5 to 12.0 to obtain a crystalline hydrate of 9-deoxo-9a-aza-9a-homoerythromycin A of formula (II); and
- 10 (b) N-methylating the compound of formula (II) prepared in step (a) with an aqueous formaldehyde-formic acid mixture in an organic solvent:





2. The method of claim 1, wherein citric acid is used in an amount ranging from 1 to 20 mole equivalents based on 1 mole of 6,9-imino ether of formula (III).
3. The method of claim 1, wherein the pH of the acidic solution is in the range of 2.0 to 3.0.
4. The method of claim 1, wherein the amount of acetone in the aqueous acetone solution is in the range of 1 to 5 ml per 1 g of the compound of formula (III), and the water to acetone volume ratio is in the range of 1 to 4.
5. The method of claim 1, wherein the organic solvent used in step (b) is selected from the group consisting of dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, methanol, ethanol, isopropanol, acetone, ethylmethylketone, isobutylmethylketone, methyl acetate, ethyl acetate, isopropyl acetate and a mixture thereof.
6. The method of claim 1, wherein the amounts of formic acid and formaldehyde used are each independently in the range of 1 to 3 mole equivalents per 1 mole of the compound of formula (II).
7. A crystalline hydrate of 9-deoxy-9a-aza-9a-homoerythromycin A of formula (II) whose powder X-ray diffraction spectrum ($I/I^\circ \geq 10$) shows peaks at 2θ values of $7.700^\circ \pm 0.2$, $8.080^\circ \pm 0.2$, $10.080^\circ \pm 0.2$, $11.440^\circ \pm 0.2$, $12.200^\circ \pm 0.2$, $13.840^\circ \pm 0.2$, $14.100^\circ \pm 0.2$, $14.520^\circ \pm 0.2$, $14.820^\circ \pm 0.2$,

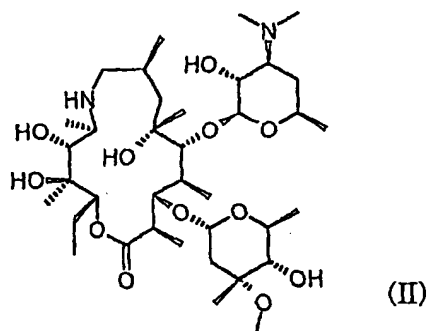
15.140° ± 0.2, 15.800° ± 0.2, 16.780° ± 0.2, 17.260° ± 0.2, 18.160° ± 0.2,
18.900° ± 0.2, 19.180° ± 0.2, 19.800° ± 0.2 and 21.040° ± 0.2:

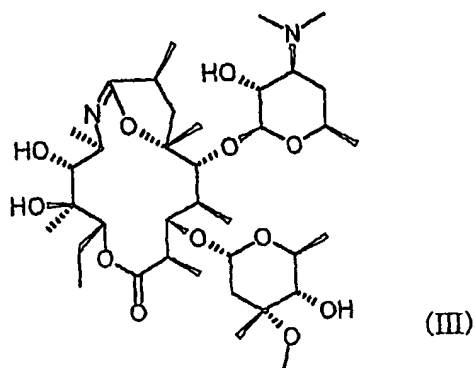


5

8. The crystalline hydrate of claim 7 which is a monohydrate.

9. A method of preparing the crystalline hydrate of claim 7 comprising the steps of: (i) reducing 6,9-imino ether of formula (III) dissolved in methanol with 5 to 7 mole equivalents of NaBH₄ at -20 to -10°C, (ii) treating the reaction mixture with an acidic aqueous acetone solution of citric acid, and (iii) adjusting the solution pH to 10.5 to 12.0:



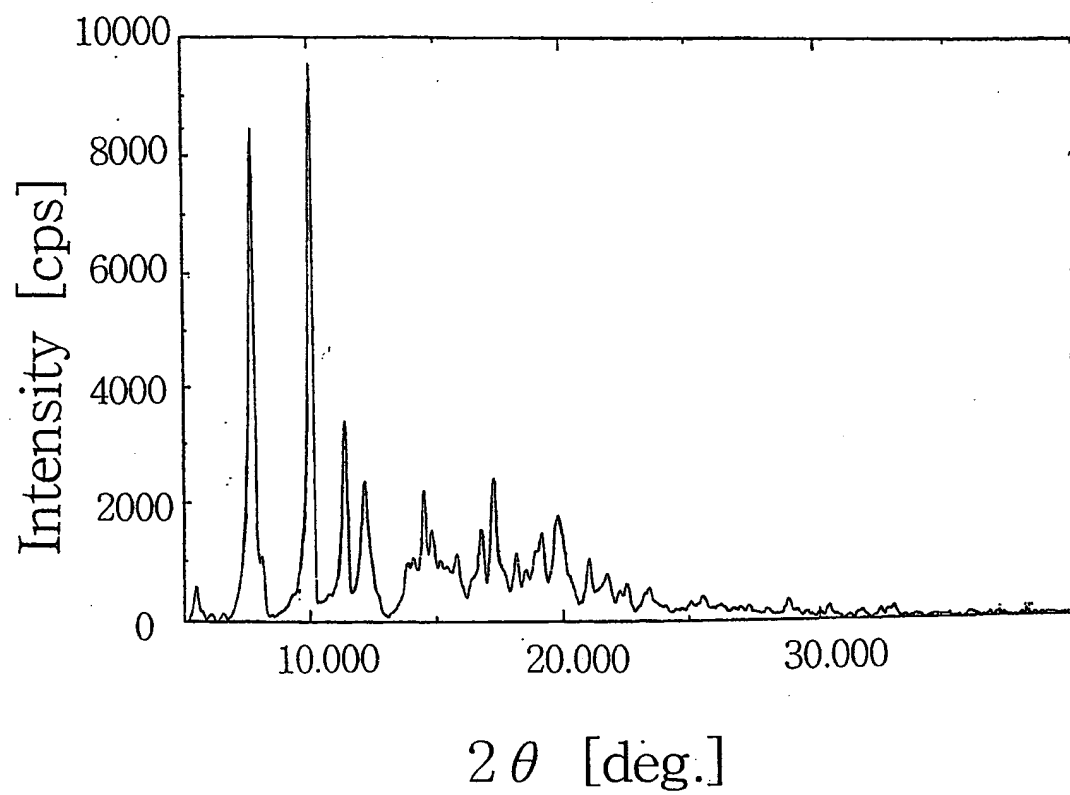


10. The method of claim 9 which further comprises the step of recrystallizing the crystalline hydrate from a mixture of water and an organic solvent selected from acetone, methanol and acetonitrile.

11. The method of claim 10, wherein the organic solvent is used in an amount ranging from 1 to 2 ml per 1 g of the crystalline hydrate, and the water to organic solvent volume ratio is in the range of 1 to 4.

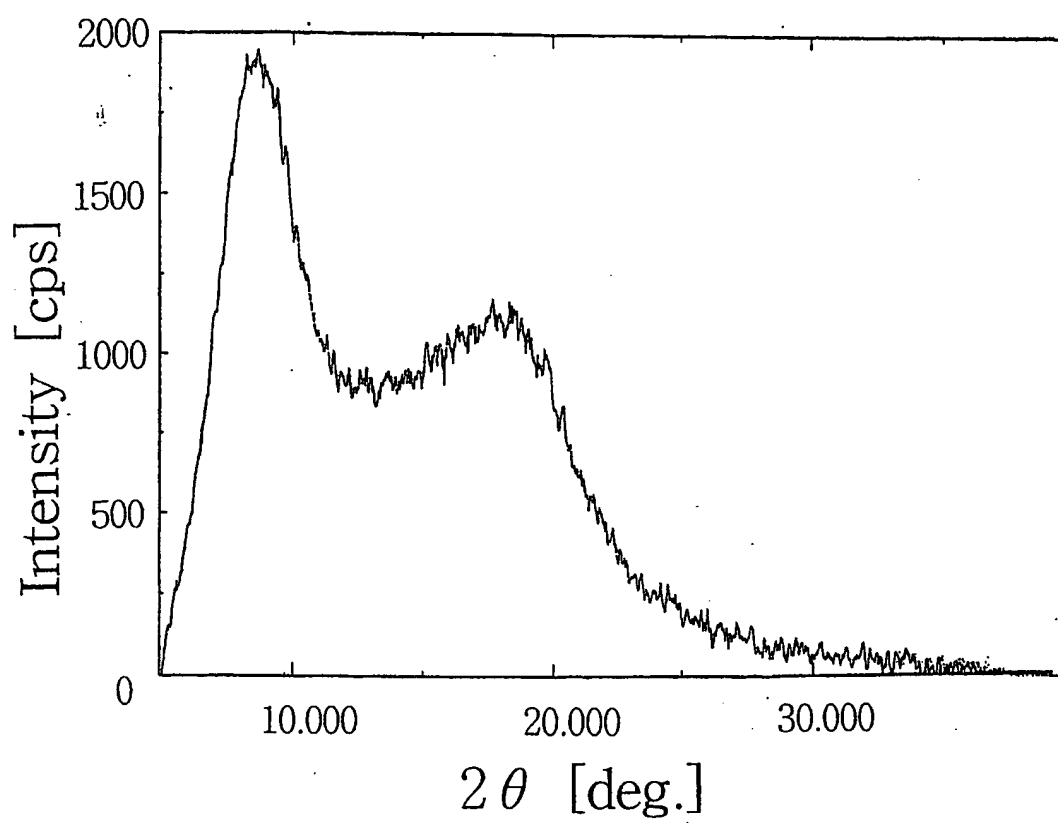
$1/2$

FIG. 1




$2/2$

FIG. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR02/00588

A. CLASSIFICATION OF SUBJECT MATTER		
IPC7 C07H 17/08		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC C07H 17/* IPC A61K 31/*		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Korean Patents and applications for inventions since 1975.		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
KIPASS, USPTO, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 298 650 A2 [PFIZER INC] 11. Jan 1989. see the whole document.	1 - 11
A	EP 0 307 128 A2 [PFIZER INC] 15. Mar 1989. see the whole document.	1 - 11
A	EP 0 941 999 A2 [HOVIONE INTER LTD] 15. Sep 1999. see the whole document.	1 - 11
A	EP 0 879 823 A1 [HOVIONE INTER LTD] 25. Nov 1998. see the whole document.	1 - 11
A	EP 0 984 020 A2 [APOTEX INC] 08. Mar 2000. see the whole document.	1 - 11
A	JP 2001-187797 A [ASTUR PHARMA S. A] 10. Jul 2001. see the whole document.	1 - 11
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>		
Date of the actual completion of the international search		Date of mailing of the international search report
24 DECEMBER 2002 (24.12.2002)		26 DECEMBER 2002 (26.12.2002)
Name and mailing address of the ISA/KR		Authorized officer
 Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140		YOU, In Kyoung Telephone No. 82-42-481-5595

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR02/00588.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0 298 650 A2	11. 01. 1989.	NONE	
EP 0 307 128 A2	15. 03. 1989.	NONE	
EP 0 941 999 A2	15. 09. 1999.	JP 11- 322776 A	24. 11. 1999
EP 0 879 823 A1	25. 11. 1998.	JP 10- 316699 A	02. 12. 1998
EP 0 984 020 A2	08. 03. 2000.	NONE	
JP 2001-187797 A	10. 07. 2001.	EP 1 103 558 A2	30. 05. 2001